

## CLAIMS: -

SUB  
D27

5 1. A multiparticulate bisoprolol formulation for once-daily oral administration, each particle comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating, said polymeric coating being effective to achieve an initial lag of bisoprolol release *in vivo* of at least 4-6 hours following administration and thereafter maintaining therapeutic concentrations of bisoprolol for the remainder of the twenty-four hour period.

10

2. A multiparticulate bisoprolol formulation according to Claim 1, wherein the polymeric coating is effective to prevent quantifiable bisoprolol plasma concentrations *in vivo* for a period of at least 3-6 hours.

15

Sub  
B1

3. A multiparticulate bisoprolol formulation according to Claim 1 or 2, which contains a pharmaceutically acceptable salt of bisoprolol.

SUB  
D320

4. A multiparticulate bisoprolol formulation according to Claim 3, wherein the salt is bisoprolol hemifumarate.

Sub  
B2

5. A multiparticulate bisoprolol formulation according to any preceding claim, which has an *in vitro* dissolution profile which when measured in a U.S. Pharmacopoeia 2 Apparatus (Paddles) in phosphate buffer at pH 6.8 at 37°C and 50 rpm substantially corresponds to the following:

25

Sub  
B24  
cont

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

(b) from 0% to 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 50% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

6. A multiparticulate bisoprolol formulation according to any preceding claim, which has an *in vitro* dissolution profile which when measured in a U.S. Pharmacopoeia 1 Apparatus (Baskets) at 37°C and 50 rpm in 0.01 N HCl for the first 2 hours followed by transfer to phosphate buffer at pH 6.8 for the remainder of the measuring period substantially corresponds to the following:

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

(b) less than 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 20% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

Sub  
B3  
cont

7. A multiparticulate bisoprolol formulation according to any preceding claim, wherein a sealant or barrier layer is applied to the core prior to the application of the polymeric coating.

Sub  
D3

8. A multiparticulate bisoprolol formulation according to Claim 7, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.

9. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the bisoprolol active ingredient is applied to a non-pareil seed having an average diameter in the range of 0.4-1.1mm.

Sub  
B3

10. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating contains a major proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of low permeability.

11. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating contains a minor proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of high permeability.

12. A multiparticulate bisoprolol formulation according to Claim 10 or 11, wherein the or each polymer is a methacrylic acid co-polymer.

*Sub B3 cont*

13. A multiparticulate bisoprolol formulation according to Claim 10 or 11, wherein the or each polymer is an ammonio methacrylate copolymer.

5 14. A multiparticulate bisoprolol formulation according to Claim 12 or 13, wherein a mixture of said polymers is used.

15 15. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating includes one or more soluble excipients so as to increase the permeability of the coating.

*Sub B4*

15 16. A multiparticulate bisoprolol formulation according to Claim 15, wherein the or each soluble excipient is selected from a soluble polymer, a surfactant, an alkali metal salt, an organic acid, a sugar and a sugar alcohol.

*Sub B4*

20 17. A multiparticulate bisoprolol formulation according to Claim 15 or 16, wherein the soluble excipient is selected from polyvinyl pyrrolidone, polyethylene glycol and mannitol.

18. A multiparticulate bisoprolol formulation according to any one of Claims 15-17, wherein the soluble excipient is used in an amount of from 1% to 10% by weight, based on the total dry weight of the polymer.

25 19. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating includes one or more

*Sub B4 cont*  
auxiliary agents selected from a filler, a plasticiser and an anti-foaming agent.

20. A multiparticulate bisoprolol formulation according to any  
5 preceding claim, wherein the coating polymer is coated to 10% to 100% weight gain on the core.

21. A multiparticulate bisoprolol formulation according to any  
10 preceding claim, wherein the coating polymer is coated to 25% to 70% weight gain on the core.

22. A multiparticulate bisoprolol formulation according to any  
preceding claim, wherein a sealant or barrier layer is applied to the polymeric coating.

*Sub B4*  
15 23. A multiparticulate bisoprolol formulation according to Claim 22, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.

20 *Sub B3*  
24. An oral dosage form containing a multiparticulate bisoprolol formulation according to any one of Claims 1-23, which is in the form of caplets, capsules, particles for suspension prior to dosing, sachets or tablets.

25. An oral dosage form according to Claim 24, which is in the form of tablets selected from disintegrating tablets, fast dissolving tablets, effervescent tablets, fast melt tablets and mini-tablets.

- before de

27. An oral dosage form according to Claim 24, substantially as hereinbefore described.

Ad  
Ar 7

Ad  
Up

項目	2000年	2001年	2002年	2003年	2004年	2005年	2006年	2007年	2008年	2009年	2010年	2011年	2012年	2013年	2014年	2015年	2016年	2017年	2018年	2019年	2020年	2021年	2022年	2023年	2024年	2025年	2026年	2027年	2028年	2029年	2030年	2031年	2032年	2033年	2034年	2035年	2036年	2037年	2038年	2039年	2040年	2041年	2042年	2043年	2044年	2045年	2046年	2047年	2048年	2049年	2050年	2051年	2052年	2053年	2054年	2055年	2056年	2057年	2058年	2059年	2060年	2061年	2062年	2063年	2064年	2065年	2066年	2067年	2068年	2069年	2070年	2071年	2072年	2073年	2074年	2075年	2076年	2077年	2078年	2079年	2080年	2081年	2082年	2083年	2084年	2085年	2086年	2087年	2088年	2089年	2090年	2091年	2092年	2093年	2094年	2095年	2096年	2097年	2098年	2099年	2100年																																																																												
人口	12,000	12,500	13,000	13,500	14,000	14,500	15,000	15,500	16,000	16,500	17,000	17,500	18,000	18,500	19,000	19,500	20,000	20,500	21,000	21,500	22,000	22,500	23,000	23,500	24,000	24,500	25,000	25,500	26,000	26,500	27,000	27,500	28,000	28,500	29,000	29,500	30,000	30,500	31,000	31,500	32,000	32,500	33,000	33,500	34,000	34,500	35,000	35,500	36,000	36,500	37,000	37,500	38,000	38,500	39,000	39,500	40,000	40,500	41,000	41,500	42,000	42,500	43,000	43,500	44,000	44,500	45,000	45,500	46,000	46,500	47,000	47,500	48,000	48,500	49,000	49,500	50,000	50,500	51,000	51,500	52,000	52,500	53,000	53,500	54,000	54,500	55,000	55,500	56,000	56,500	57,000	57,500	58,000	58,500	59,000	59,500	60,000	60,500	61,000	61,500	62,000	62,500	63,000	63,500	64,000	64,500	65,000	65,500	66,000	66,500	67,000	67,500	68,000	68,500	69,000	69,500	70,000	70,500	71,000	71,500	72,000	72,500	73,000	73,500	74,000	74,500	75,000	75,500	76,000	76,500	77,000	77,500	78,000	78,500	79,000	79,500	80,000	80,500	81,000	81,500	82,000	82,500	83,000	83,500	84,000	84,500	85,000	85,500	86,000	86,500	87,000	87,500	88,000	88,500	89,000	89,500	90,000	90,500	91,000	91,500	92,000	92,500	93,000	93,500	94,000	94,500	95,000	95,500	96,000	96,500	97,000	97,500	98,000	98,500	99,000	99,500	100,000